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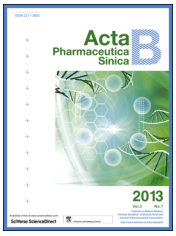

ORIGINAL ARTICLE

A novel translabial platform utilizing bioexcipients from *Litchi chinesis* for the delivery of rosiglitazone maleate

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KEY WORDS

Translabial;
Rosiglitazone;
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Strip;
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Abstract The aim of this study was to formulate drug-loaded bio-lipstrips using novel bioexcipients isolated from the fruit pulp of *Litchi chinesis* (biomaterial L) and to explore the potentiality of lip skin as a novel translabial drug delivery system. The biomaterial, prepared by a simplified economical process and purified by hot dialysis, was subjected to various physicochemical evaluations along with spectral analysis including UV, FT-IR, Mass and ^{1}H NMR. The lipstrip formulated with the novel bioexcipients was screened for its functional properties, including filmability using a film-casting method, and bio/muco-adhesitivity using a shear-stress method, the Park and Robinson method and a rotating cylinder method. Rosiglitazone-loaded bio-lipstrips were formulated by using biomaterial L as a strip former and dextrose as a flexicizer. The formulated strips were subjected to various evaluations, including thickness, folding endurance, *in-vitro* release and *in-vivo* release. The release of rosiglitazone maleate was maintained over 24 h, which was confirmed in *in-vitro* and *in-vivo* release experiments. Our results reveal that this biopolymer possesses promising stripability as well as bio-adhesitivity. The formulated bio-lipstrips are feasible for delivering rosiglitazone maleate by translabial administration.

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1. Introduction

The skin of lips is unique. It lacks infrastructure, making it pliable. It consists primarily of mucous membrane, which has fewer and different glands than ordinary skin. The lip is also unlike other skin in that the outer layer (stratum corneum) is extremely thin or completely absent in most people. Lips also have almost no melanin, the natural pigment in skin that helps screen out the sun's harmful rays. The translabial application of drugs provides several benefits, including the avoidance of hepatic first-pass metabolism and the ability to provide nearly constant drug delivery over a long period, which may reduce systemic adverse effects[1–4]. The skin forms an excellent barrier against drug permeation due to the rigid lamellar structure of the stratum corneum lipids. Our novel translabial drug delivery sidesteps this barrier due to very thin or absent layers of stratum corneum.

Rosiglitazone maleate belongs to the drug class of thiazolidinediones. It is a selective agonist for peroxisome proliferator-activated receptor gamma (PPARγ)[5] and particularly suitable for diabetic patients who are overweight and for whom metformin is contraindicated[6,7]. Rosiglitazone reduces fasting and postprandial glucose levels and effectively lowers plasma insulin and triglyceride levels[8]. It regulates the transcription of certain insulin-responsive genes and subsequently improves insulin sensitivity and controls glucose production, transport and utilization[9]. The drug has a log P value of 2.1, which contributes to its lipid solubility and hydrophilicity. However, rosiglitazone is metabolized extensively by *N*-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid in the liver with an elimination half-life of 3–5 h[10], necessitating frequent administration. Recently, a study has indicated that sustained delivery of rosiglitazone through a transdermal route can help avoid toxicity due to a sudden high blood concentration. This study was undertaken to screen the potential of rosiglitazone maleate for transdermal delivery.

Natural polysaccharides from biomaterials have been widely used as bioadhesive materials because of their biocompatibility and biodegradability. The *Litchi chinesis* biomaterial (biomaterial L) used in this study was isolated from the pulp of a subtropical evergreen tree *Lichi chinesis*, which belongs to the family of Sapindaceae. The pulp of lichi contains carbohydrate, dietary fiber, fat, protein, vitamin C and minerals[11]. *Litchi chinensis* has been reported to have anti-inflammatory, antioxidant antidiabetic, antiplatelet and anticoagulant activities[12]. In our research work, biomaterial L was used as a bioadhesive and strip-forming agent in the dosage form.

The aim of our research was to isolate biomaterial L, formulate lipstrips using this material, evaluate its bioadhesitivity and strip-forming capability, and determine the suitability of bio-lipstrips as a drug delivery method for rosiglitazone maleate.

2. Materials and methods

2.1. Materials

Rosiglitazone maleate (assigned purity, 99.8%) was a gift from Sun Pharma (Mumbai, India). Ripened fruits of *Litchi chinesis* were purchased from the market of Dehradun, Uttarakhand, India. Sodium carboxy methylcellulose (CMC-Na) and HPMC were purchased from Merck Specialties Private Limited. (Mumbai, India). All other chemicals and solvents were of analytical grade.

2.2. Isolation of biomaterial L

Litchi chinesis fruits (ripened) were collected from the local market and the pulps were separated from the fruits. *Litchi chinesis* pulps (100 g) were treated with 500 mL of doubly-distilled water and stirred with a mechanical stirrer at 4000 rpm for 1 h. The mixture was subjected to centrifugation at 4000 rpm for 30 min. The supernatant was treated with a triple volume of acetone and the mixture was refrigerated for 12 h, after which the mixture was centrifuged at 5000 rpm for 30 min. The supernatant was discarded and the insoluble material was dried in a vacuum desiccator for 14 h. The dried biomaterial was purified by the hot dialysis method using an ORCHID scientific dialysis apparatus for complete removal of impurities like chlorides and sulfates. The procedure was optimized by repeating the procedure 6 times and the percentage yield was calculated. The purified biomaterial L was screened through 200# mesh and stored for later use.

2.3. Preparation of bioadhesive lipstrips

Biopolymer L (100 mg) was placed in a mortar and 110 mg of dextrose was added. Both were triturated for 5 min, after which 5 mg of rosiglitazone maleate was incorporated in a geometrical dilution pattern. Doubly-distilled water (10 mL) was added dropwise with constant trituration. The mixture was subjected to magnetic stirring for 10 min and sonicated at 400 Hz for 3 cycles of 60 s each in order to obtain a colloidal mixture. The colloidal mixture was poured into a culture dish with a diameter of 6 cm and was evaporated at room temperature for 10 h, allowing a dried layer to form. The layer was carefully removed and cut into 2 cm × 2 cm squares. Ethyl cellulose was used as a backing membrane. A similar procedure was adopted for other concentrations of biopolymer L, CMC-Na and sodium alginate polymers (Table 1).

2.4. Characterization of biomaterial L

The isolated biomaterial L was subjected to physicochemical analysis, including solubility, color changing point, color, texture, protein and carbohydrate content, SEM analysis and FT-IR, mass spectrometry and ^{1}H NMR spectroscopy studies.

It was further evaluated for its adhesitivity by using a shear stress method, the Park and Robinson method and a rotating cylinder method. The results were compared with the commonly used adhesive materials, CMC-Na and HPMC.

2.4.1. In-vitro adhesive study using the shear stress method

The mucoadhesive properties of biomaterial L was determined *in vitro* by the shear stress method. Three different concentrations of biomaterial L (1%, 3% and 5% *w/v*) were placed between two glass plates and subjected to a shear stress for assessment for *in-vitro* adhesive strength in terms of weight required for breaking adhesive bonds between the material and the glass plate after a specified contact time of 5, 10, 15 and 30 min. The results were compared with polymer CMC-Na (1%)[13].

2.4.2. Ex-vivo mucoadhesive studies

2.4.2.1. Park and Robinson method. Goat intestine membrane was used to assess the mucoadhesivity of biomaterial L by Park and Robinson method. The biomaterial L was compressed into a

Table 1 Formulation of various bio-lipstrips.

Serial no.	Ingredient	SA1	SA2	LA1	LA2	LA3	LA4	LA5	LA6
1	Rosiglitazone maleate (mg)	5	5	5	5	5	5	5	5
2	*Litchi chinesis* (L.) biopolymer (mg)	–	–	100 (1%)	200 (2%)	300 (3%)	400 (4%)	500 (5%)	600 (6%)
3	Sodium carboxy methyl cellulose (mg)	400 (4%)	–	–	–	–	–	–	–
4	Sodium alginate (mg)	–	400 (4%)	–	–	–	–	–	–
5	Dextrose (mg)	110	110	110	110	110	110	110	110
6	Double distilled water (mL)	10	10	10	10	10	10	10	10

small circular disc. The prepared circular disc containing biomaterial L were lightly pressed for 10 min between the mucosal surfaces of goat intestine which was tied to the mouth of a glass vessel and a cap connected with a weight measurement device. The detachment force required to separate the disc from mucosal surface was measured in triplicate and the results were compared with the commonly used polymers like CMC-Na and HPMC[14].

2.4.2.2. Rotating cylinder method. The length of adhesion of biomaterial L compressed on a disc to goat intestinal membrane was evaluated by the rotating cylinder method using a USP Type-II dissolution apparatus. The freshly prepared intestinal membrane was attached to the cylindrical basket. The compressed disc was carefully adhered to the membrane by prior wetting with water. The cylinders were positioned in the basket containing 900 mL of phosphate buffer at pH 7.4 at 37 ± 2 °C. The study was conducted at a speed of 100 rpm. The disc was observed at different time intervals. The time required for dislodgment and/or disintegration of disc was recorded and the study was conducted in triplicates. The results were compared with the commonly used polymers like CMC-Na and HPMC[15].

2.5. Drug–excipient interaction study

The pure drug along with formulation excipients was subjected to interaction studies.

2.5.1. UV spectroscopy

The study was carried out by dry and wet mixing of drug and excipients in the ratios of 1:1, 1:3 and 3:1. Both types of mixtures were stored at room temperature and at 55 °C for three days. The appropriate dilutions were done with methanol and pH 7.4 phosphate buffer and the samples were scanned at λ_{max} using UV spectroscopy.

2.5.2. FT-IR spectroscopy

The study was performed using FT-IR spectroscopy by mixing or finely grinding various proportions of drug and excipients with a specially purified salt (potassium bromide) to remove scattering effects from large crystals. The powder mixture was then pressed in a mechanical press to form a translucent pellet through which the beam of the spectrometer could pass.

2.6. Characterization of drug-loaded bio-lipstrips

2.6.1. Thickness

The thickness of three randomly selected bio-lipstrips was assessed at five different places (the center and four corners) on a single patch of each formulation using a micrometer screw gauge and the mean values were calculated[16].

2.6.2. Weight uniformity study

Three bio-lipstrips with the surface area of 1 cm^2 were randomly selected from each formulation. Each strip was weighed and the study was performed in triplicate and average weights were calculated[16,17].

2.6.3. Content uniformity

Formulated drug-loaded bio-lipstrips were evaluated for uniformity of drug content. Strips of 1 cm^2 from each formulation were randomly selected and transferred into a 100 mL volumetric flask containing 7 mL pH 7.4 phosphate buffer and 1 mL methanol. The flask was stirred for 4 h on magnetic stirrer. A blank control was similarly prepared using a drug-free strip. The obtained solutions were filtered through a 0.45 µm membrane. The drug content was then determined after proper dilution by UV spectrophotometry (Shimadzu 1800)[16,17].

2.6.4. Folding endurance

Folding endurance for all bio-lipstrips containing rosiglitazone was performed by using a strip with area of 4 cm^2 from each formulation. The selected bio-lipstrips were subjected to folding endurance by repeatedly folding strips at the same place until broken. The number of foldings required to break or crack a strip was recorded as the folding endurance[18,19]. The measurement was repeated in triplicate.

2.6.5. Swelling index

Drug-loaded bio-strips with a size of 1 cm^2 from each formulation were selected for the swelling study. Each bio-lipstrip was weighed on a cover slip and placed in a culture dish and 10 mL of phosphate buffer of pH 7.4 was added. After one hour the cover slip with bio-lipstrip was weighed. The difference in the weights gives the weight increase due to absorption of water and swelling of bio-film. The procedure was repeated in triplicate and the swelling index (S) was determined by Eq. (1).

$$S(\%) = (X_t – X_0/X_0) \times 100\% \quad (1)$$

where X_t is the weight of the swollen bio-strip after time t and X_0 is the original weight of bio-strip[20].

2.6.6. Percentage moisture absorption (PMA)

A percent moisture absorption study for all formulated bio-lipstrips was conducted with 1 cm^2 of rosiglitazone-loaded bio-lipstrips. The bio-lipstrips were transferred into a watch glass and placed in a dessicator containing a saturated solution of aluminum chloride

for 72 h. The weight gained by the strip was determined. The study was repeated thrice and the percentage moisture absorption calculated by using the following formula[21]:

$$\text{Moisture absorption (\%)} = [(\text{final weight} - \text{initial weight})/\text{initial weight}] \times 100\% \quad (2)$$

2.6.7. Percentage moisture loss (PML)

A percentage moisture loss study for all formulated bio-lipstrips was performed by taking three 1 cm^2 strips from each formulation. The strips were cut out and weighed and kept in desiccator containing fused anhydrous calcium chloride for 72 h. At the end, the weight loss by the strips was determined. The study was repeated thrice and percentage moisture loss calculated by using the following formula (3)[21]:

$$\text{Moisture loss (\%)} = [(\text{initial weight} - \text{final weight})/\text{initial weight}] \times 100\% \quad (3)$$

2.6.8. Surface pH study

The surface pH of the bio-lipstrips containing rosiglitazone was determined by using a glass electrode. The bio-lipstrips were allowed to swell by keeping them in contact with 0.5 mL of distilled water for 1 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the bio-strip and allowing it to equilibrate for 1 min. The experiments were performed in triplicate and average values were noted[22].

2.6.9. Water vapor transmission test (WVT)

WVT is defined as the quantity of moisture transmitted through a unit area of strip in unit time. A glass bottle (length of 5 cm, narrow mouth with internal diameter of 0.8 cm) filled with 2 g anhydrous calcium chloride and an adhesive (Feviquick®) spread across its rim was used in the study. The bio-strip was fixed over the adhesive and the assembly was placed in a sealed desiccator containing 200 mL of saturated sodium bromide and saturated potassium chloride solution. The weighed bottle was then placed in a desiccator and the procedure was repeated[23,24].

$$\text{WVT} = W/ST \quad (4)$$

where W is the increase in weight in 24 h; S is area of strip exposed (cm^2); T is exposure time.

2.6.10. Skin irritancy

Primary skin irritation studies were conducted for the two best-optimized patches on four rabbits. Rabbits were divided into two groups of two animals. A blank strip was applied on the lip of rabbits of group I, which served as control, and rabbits of group II received medicated strips on their lip. Strips were replaced after 6 h with fresh strips. The study was carried out for a period of 7 days and application sites were visually graded for redness, erythematosis or irritation[25].

2.6.11. In-vitro diffusion study

The *in-vitro* drug diffusion assay was carried out in the M.S. diffusion apparatus. This was the static method and employed complete replacement of the sample. Dialysis membrane was tied to the terminal portion of the cylindrical donor compartment. A 1 cm^2 bio-lipstrip was kept above the dialysis membrane in the donor compartment, and the receiver compartment was filled with 13 mL of diffusion medium. The complete sample was withdrawn at different time intervals and the receiver compartment was refilled with 13 mL of fresh medium. The amount of drug released was assessed by measuring the absorbance at 247 nm using a UV spectrophotometer (Shimadzu 1800).

2.6.12. In-vivo release study

The *in-vivo* release was performed in rabbits for the optimized formulation. The bio-lipstrip was applied to the lip of rabbit and blood samples were taken from the ear vein at intervals of 2, 6, 10, 12 and 24 h to determine the concentration of drug in the blood plasma. Plasma was separated immediately by centrifugation at 3000 × g for 10 min. The plasma was treated with 5 mL HPLC-grade methanol, subjected to sonication for 5 cycles, and filtered through a membrane filter. The drug content was estimated by injecting the filtrate into the HPLC column using methanol and phosphate buffer of pH 7.4 as mobile phase and at a rate of 1.2 mL/min[22].

2.6.13. Stability studies

Optimized bio-lipstrip was subjected to a stability study. Bio-strips were wrapped in aluminum foil and packed in glass vials. These strips were kept in an incubator maintained at 37 ± 5 °C and 75 ± 5% R.H. for 6 months. The changes in appearance, physical characteristics and release behavior of the stored strips were investigated after 1–6 months. The data presented are the mean of three determinants[23].

3. Results and discussion

3.1. Spectral analysis of the biomaterial L

The isolated biomaterial L was smooth, amorphous, yellowish white and slightly soluble in water. The yield was found to be 1.85 ± 0.05% *w/w*. The biomaterial L showed a positive test for Fehling's solution and a positive ninhydrin test, which revealed the presence of carbohydrate and protein, respectively. The color changing point and λ_{max} for biomaterial L was found to be 255 °C and 290 nm, respectively. The IR spectra revealed the presence of secondary alcohol (1099.83 cm^{-1}), aromatic nitro and phenol groups (1316.59 cm^{-1}), aromatic rings (1544.70 cm^{-1}), and the presence of alkenes (1652.02 cm^{-1}), with –CH_2 and –COOH stretching (2928.35 cm^{-1}) along with β-diketones and O–NO_2 (1652.02 cm^{-1}) (Fig. 1). These functional groups, such as ketonic and nitro groups, are likely responsible for the mucoadhesive activity of the bio-polymer as these groups are observed in mucoadhesive polymers like HPMC and polycarbophil. The NMR spectra showed δ values 1.2, 2.3 and 6.4, which revealed the presence of hydroxyl, esters and aromatic groups,

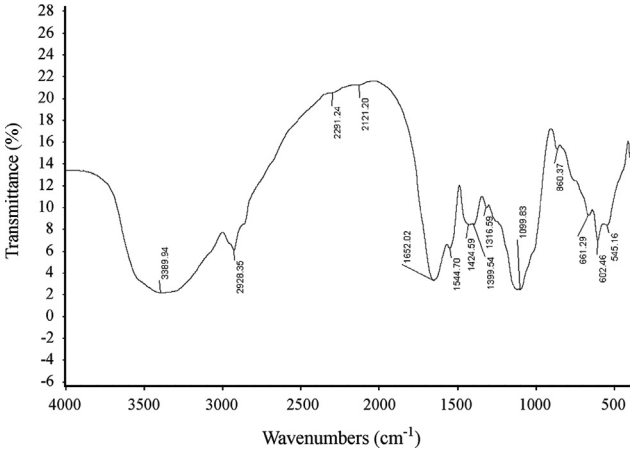

Figure 1 IR spectrum of isolated biomaterial L.

respectively (Fig. 2). The mass spectrum shows a large molecular weight structure likely polymeric, and the presence of proteins. It showed a parent peak at *m/z* 345.1 (Fig. 3).

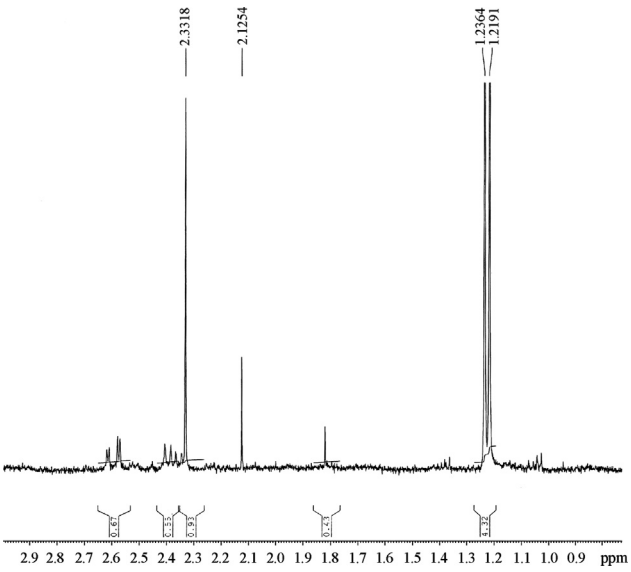

Figure 2 ^{1}H NMR spectrum of isolated biomaterial L.

3.2. *SEM of biomaterial L*

The topography of the biomaterial L revealed that it has rough, flaky structure with additional granular structure on the flaky surface. This clearly indicates it is slightly granular and polymeric in nature (Fig. 4).

3.3. *Adhesitivity of biopolymer L*

The study of adhesitivity (Figs. 5, 6 and 7) showed that the biomaterial L has significant adhesitivity in comparison with CMC-Na and HPMC. The result of adhesitivity test revealed that the isolated biomaterial L from the pulp of *Litchi chinesis* possesses notable muco/bio-adhesitivity.

3.4. *Drug–excipient interaction study*

The drug interaction study revealed that there was no interaction between the drug and the excipients, including the biomaterial L, because there was no change in the λ_{max} value, which was observed at 247 nm prior to and after the test.

All the FT-IR peaks of rosiglitazone maleate were present as such in the spectra of ground drug and excipient mixture. No observable signs of drug interaction were observed. We conclude that the excipients had no detrimental effect on the drug and could be used safely for the formulation of the bio-films.

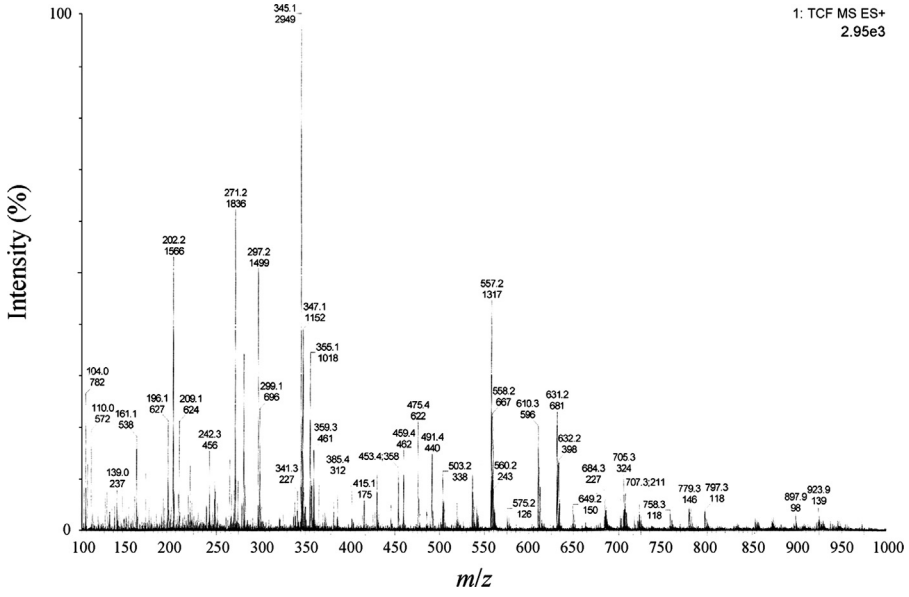

Figure 3 Mass spectrum of isolated biomaterial L.

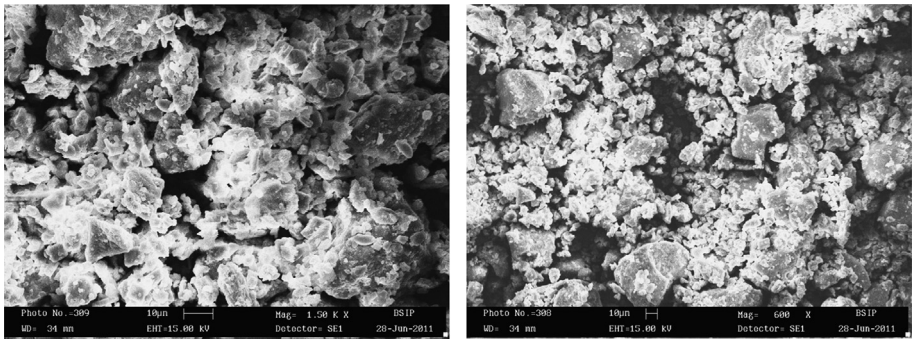

Figure 4 SEM of isolated biomaterial L. (A) 1500 × and (B) 600 × .

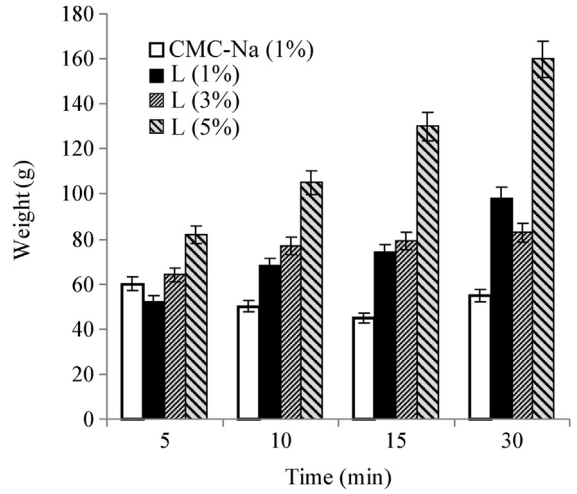

Figure 5 *In-vitro* mucoadhesivity evaluated by shear stress method. L: Biomaterial L.

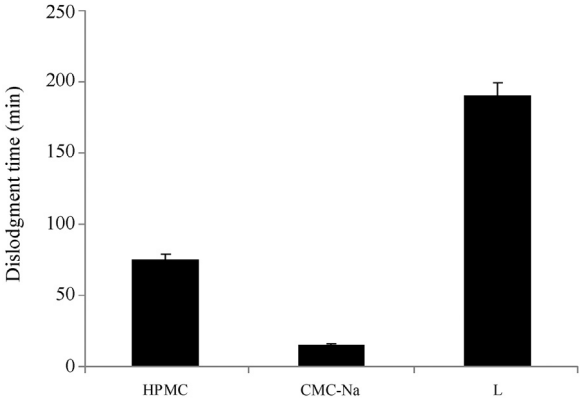

Figure 6 *Ex-vivo* mucoadhesivity evaluated by rotating cylinder method. L: Biomaterial L.

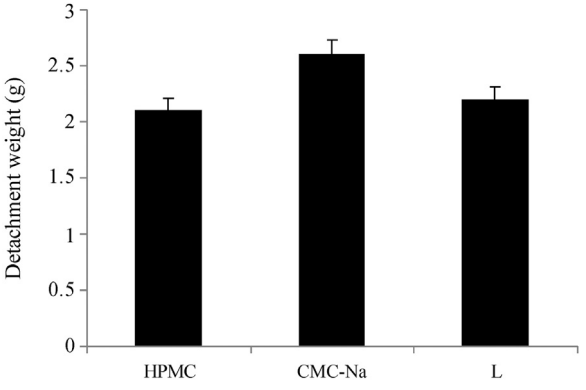

Figure 7 *Ex-vivo* mucoadhesivity evaluated by Park and Robinson method. L: Biomaterial L.

3.5. Thickness, swelling index, surface pH and folding endurance

The average thickness of all prepared bio-lipstrips ranged 0.36 ± 0.03 to 0.46 ± 0.07 mm. Weight variation values of all strips (1 cm^2) were found in the range 28.75 ± 0.23 to 39.93 ± 0.37 mg. Thus, the proportional gain in the weight of strips was observed as the thickness of the strips increased. The values were uniform for the strips within each formulation type, indicating that the strip casting was uniform.

The range of the swelling index for the bio-strips was found to be 101.33 ± 0.54 to 153.75 ± 0.61. The swelling index suggests that they will cause minimal discomfort when in use. This property of the strip has a direct influence on release of drug.

The surface pH for all formulations was found to range from 6.32 ± 0.31 to 6.52 ± 0.43. Since the pH range of the strip was close to the skin pH, no skin irritation was expected.

The folding endurance of strips fell in the range 119 ± 0.56 to 194 ± 0.48. High folding endurance values for strips indicates high mechanical strength of strips. This is highly desirable because it would prevent dislocation of the strips from the site of application or breaking of the strip during administration.

3.6. Skin irritation, moisture content, moisture uptake, WVT and content uniformity

No skin irritation, redness or erythema was observed during the primary skin irritation studies with all formulations.

The moisture content of the prepared formulation was low, which could help the formulation remain stable and reduce brittleness during long term storage. The moisture content of the bio-strips ranged from $0.92 \pm 0.08\%$ to $1.38 \pm 0.15\%$.

Moisture uptake for the bio-strips ranged from $3.28 \pm 0.21\%$ to $4.96 \pm 0.39\%$. The moisture uptake of the formulation was low, which protects the formulation from microbial contamination and reduces bulkiness.

The range of WVT for the bio-strips was found to be 4.81 ± 0.41 to 7.40 ± 0.53.

The range of content uniformity for the bio-strips was found to be between $91.58 \pm 0.81\%$ to $96.4 \pm 0.74\%$. There was no significant difference in the drug content among the all bio-lipstrips, which indicated uniform dispersion of drug throughout the strips.

3.7. In-vitro release

The *in-vitro* release of rosiglitazone from the different strips is shown in Fig. 8. All the formulations released $>90\%$ of the drug within 10 h. Formulation LA2 showed the maximum release of 99.81% at the end of 24 h. Formulation LA4 showed the slowest drug release, and showed maximum drug release of 96.98% after 24 h. We could not detect any relationship between the drug release profile and the polymer composition. We can only infer that the release mechanism might include diffusion as well as erosion, since our biomaterial is slightly soluble in water. The release data of the tested strips was analyzed on the basis of the Krosmeyer–Peppas equation and Higuchi kinetics (by BIT-SOFT 1.12: drug release kinetics with model fitting). Coefficients of correlation (R^2) were used to evaluate the accuracy of fit. The R^2 values for the Higuchi and Peppas kinetic models were calculated and compared. All the tested formulations gave good fit to the Krosmeyer–Peppas model. All formulations showed non-Fickian drug release ($0.5 < n < 1$). On the basis of the above determinations, LA3 was selected as the best formulation.

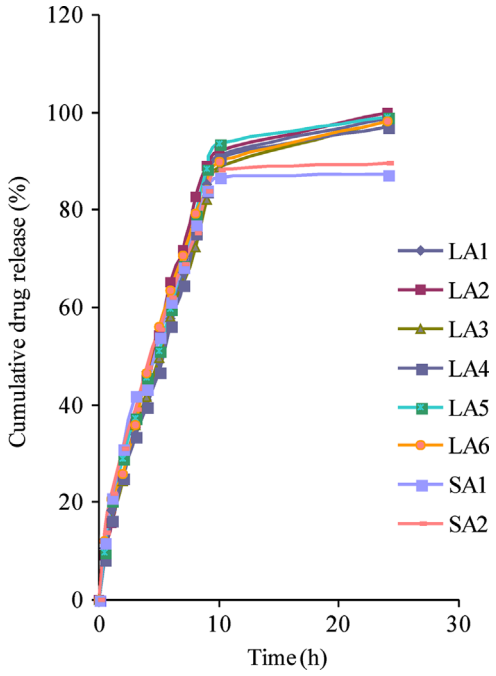

Figure 8 *In-vitro* release of rosiglitazone from bio-lipstrips with different concentration of biomaterial L (1–6%) compared with strips with CMC-Na (4%) and sodium alginate (4%).

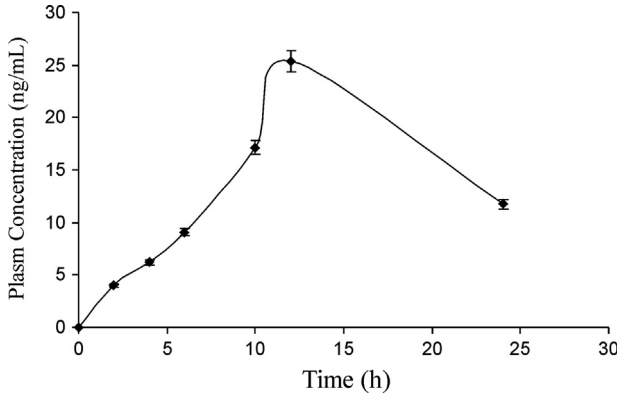

Figure 9 *In-vivo* release of rosiglitazone from translibially administered bio-lipstrips in rabbit plasma.

3.8. Stability study

At the end of stability study, the tested strips showed little to no drug loss. They also showed an insignificant difference for *in-vitro* drug release. All optimized strips showed satisfactory flexibility and elastic properties during and at the end of the accelerated stability period. These indicate that there were no influences on the chemical and physical stability of the formulation during the test period.

3.9. In vivo study

Translabial administration of LA3 bio-lipstrip achieved a C_{max} of rosiglitazone of 23.084 ng/mL at a T_{max} of 12 h. The $AUC_{0-24\ h}$ was found to be 336.55 ng·h/mL (Fig. 9). The results indicated that rosiglitazone can enter the blood circulation *via* labial route, proving that it can be an option when consider transdermal delivery.

4. Conclusions

In the present study, bioadhesive bio-lipstrips based on *Lichi chinesis* biomaterial were developed and shown to release drug over the required period of time (12 h). Thus, a stable bioadhesive bio-lipstrip of rosiglitazone for the treatment of diabetes using this novel biomaterial was demonstrated. The biomaterial showed good strip-forming ability as well as satisfactory bioadhesion. Thus, this natural biomaterial could be a promising excipient for the systemic delivery of drugs through a labial route or other transdermal routes.

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References

1. Barry BW. Dermatological formulations: percutaneous absorption. New York: Marcel Dekker; 1983, p. 127–213.
2. Chien YW. Advances in transdermal systemic medication. In: Chien YW, editor. *Transdermal controlled systemic medications*. New York: Marcel Dekker; 1987, p. 1–24.
3. Dittgen M. Transdermal therapeutics system. In: Muller RH, Hildebrand GE, editors. *Pharmazeutische technologie: modern Arzneiformen*. Stuttgart: Wissenschaftliche Verlagsgesellschaft Stuttgart; 1997, p. 81–104; 2002, 661–8.
4. Schaefer H, Redelmeier TE. *Skin barrier: principles of percutaneous absorption*. Basle: Karger; 1996, p. 213–62.
5. Sweetman SC, Royal Pharmaceutical Society of Great Britain. *Martindale: the complete drug reference*. London: Pharmaceutical Press; 2005, p. 345.2.
6. Henry RR. Thiazolidinediones. *Endocrinol Metab Clin North Am* 1997;**26**:553–73.
7. Krentz AJ, Bailey CJ, Melande A. Thiazolidinediones for type-2 diabetes. *BMJ* 2000;**21**:252.
8. Iwamoto Y, Kuzuya T, Matsuda A, Awata T, Kumakura S, Inooka G, et al. Effect of new oral antidiabetic agent CS-045 on glucose tolerance and insulin secretion in patients with NIDDM. *Diabetes Care* 1991;**14**:1083–6.
9. Cox PJ, Ryan DA, Hollis FJ, Harris AM, Miller AK, Vousden M, et al. Absorption, disposition and metabolism of rosiglitazone, a potent thiazolidinedione insulin sensitizer, in human. *Drug Metab Dispos* 2000;**28**:772–80.
10. Hruska MW, Frye RF. Simplified method for determination of rosiglitazone in human plasma. *J Chromatogr* 2004;**80**:317–20.
11. USDA. Litchis, raw [lychee]. Available from: ⟨http://www.nutritiondata.com/facts/fruits-and-fruit-Juices/1945/2⟩ (retrieved 30.06.09).
12. Sung YY, Yang WK, Kim HK. Antiplatelet anticoagulant and fibrinolytic effects of *Litchi chinensis* Sonn. extract. *Mol Med Rep* 2012;**5**:721–4.
13. Jiménez-Castellanos MR, Zia H, Rhodesa CT. Design and testing *in-vitro* of a bioadhesive and floating drug delivery system for oral application. *Int J Pharm* 1994;**105**:65–70.
14. Park H, Robinson JR. Physicochemical properties of water insoluble polymers important to mucin/epithelial adhesion. *J Control Release* 1985;**2**:45–57.
15. Grabovac V, Guggi D, Bernkop-Schnürch A. Comparison of the mucoadhesive properties of various polymers. *Adv Drug Deliv Rev* 2005;**57**:1713–23.

16. Gattani SG, Gaud RS, Chaturvedi SC. Formulation and evaluation of transdermal films of chlorpheniramine maleate. *Indian Drugs* 2007;**44**:27–33.
17. Rao RP, Divan PV. Influence of casting solvent on permeability of ethyl cellulose free films for transdermal use. *East Pharma* 1997;**40**:135–7.
18. Kusum DV, Saisivam S, Maria GR, Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. *Drug Dev Ind Pharm* 2003;**29**:495–503.
19. Nafee NA, Boraie MA, Ismail FA, Mortada LM. Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. *Acta Pharm* 2003;**53**:199–212.
20. Wang Y, Challa P, Epstein DL, Yuan F. Controlled release of ethacrynic acid from poly(lactide-*co*-glycolide) films for glaucoma treatment. *Biomaterials* 2004;**25**:4279–85.
21. Gannu R, Vishnu YV, Kishan V, Rao YM. Development of nitrendipine transdermal patches: *in vitro* and *ex vivo* characterization. *Curr Drug Deliv* 2007;**4**:69–76.
22. Bottenberg P, Cleymaet R, de Muynck C, Remon JP, Coomans D, Michotte Y, et al. Development and testing of bioadhesive fluoride containing slow release tablets for oral use. *J Pharm Pharmacol* 1991;**43**:457–64.
23. Baichwal MR. Polymer films as drug delivery systems. In: *Advances in drug delivery systems*. Bombay: MSR Foundation; 1985, p. 136–147.
24. Zupan JA [Inventor]. Use of eucalyptol for enhancing skin permeation of bioaffecting agents. Europe Patent EP0069385 A2. 6 July 1983.
25. Drazie JH, Woodward G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J Pharmacol Exp Ther* 1944;**82**:377–9.